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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,976	ENGEL ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

1. Applicant's election with traverse of Group 1, claims 1-16 in the reply filed on June 21, 2006 is acknowledged. The traversal is on the ground(s) that the claims 17-22 of Group II all relate directly to the method of coamplification of group I and do not represent separate or distinct inventions. This is not found persuasive because as established in the previously filed restriction requirement, the amplification reaction mixtures and device(s) of group II can be used in methods that are separate and distinct from the method of coamplification claimed in the invention of group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 17-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 21, 2006.

3. Claims 1-16 are pending and will be examined.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on March 9, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3-4, 9-11 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claims 3 and 4, the inclusion of the term 'hot start DNA polymerase' is vague and indefinite. The term 'hot start' is a term of art and may be interpreted as reading on a variety of methods of supplementing or enhancing amplification specificity, including physical partitioning of reagents, modification of polymerase enzymes, or the inclusion of a reversibly inhibitory antibody directed against the DNA polymerase. Clarification of the intended metes and bounds of this limitation is requested.

8. Regarding claims 9-11 and 13-15, the inclusion of the term "has a molecular weight in the range of" followed by two numbers, without a designation of how the molecular weight is measured is vague and indefinite. Is the molecular weight intended defined by daltons, kilodaltons? Clarification of the intended unit of measure of molecular weight is requested.

Claim Interpretation

The term 'hot start DNA polymerase' was not explicitly defined within the specification. Instead, the term was broadly referred to as "the same effect was also observed with enzymes which are either temporarily chemically activated such as HotStarTaq (Qiagen GmbH) as well as with antibody-blocked enzymes (data not shown)." (p. 12, paragraph 152 of PgPub). Therefore, the term is being interpreted as reading on an enzyme such as HotStarTaq in addition to enzymes

which are complexed with anti-Taq polymerase enzymes as part of the amplification reaction or composition.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backus et al. (US Patent 5,703,366; January 1998) in view of Bustin, SA (Journal of Molecular Endocrinology, 2000, vol. 25, p. 169-193). Backus discloses a method of amplification of multiple target nucleic acids in the presence of a nonionic, polymeric volume exclusion agent (Abstract).

With regard to claim 1, Backus teaches a method for the coamplification of two or more target nucleic acids having different sequence compositions, said method comprising at least 15 primary amplification cycles (col. 2, line 67 to col. 3, line 3), each amplification cycle comprising the sequential steps of:

(A) heating a reaction mixture of two or more target nucleic acids, or their primer extension products, at a first temperature, T1, for denaturation of the strands of the target nucleic acids or their primer extension products (col. 3, lines 4-8), and

(B) priming the denatured strands with a set of unmodified or modified primers specific to and hybridizable with opposing strands of each target nucleic acid to be amplified, by cooling to a

second temperature, T2 (col. 3, lines 9-12), and

(C) either as a continuation of step (B) or in a separate step, forming primer extension products in a reaction mixture of PCR reagents, by incubation at a third temperature, T3, provided that when priming and primer extension product formation are carried out in the same step, T2 and T3 are the same (col. 3, lines 13-18),

wherein the reaction mixture in at least one of the primary amplification cycles comprises from 1 to 20 weight %, preferably from 1 to 15 weight % and most preferably from 1 to 8 weight % of a nonionic polymeric volume exclusion agent (col. 3, lines 19-21, where the disclosed percentage of 4 weight % falls within the range(s) claimed).

With regard to claim 3, Backus teaches a method for the coamplification of two or more target nucleic acids having different sequence compositions, said method comprising at least 15 primary amplification cycles (col. 2, line 67 to col. 3, line 3), each amplification cycle comprising the sequential steps of:

(A) heating a reaction mixture of two or more target nucleic acids, or their primer extension products, at a first temperature, T1, for denaturation of the strands of the target nucleic acids or their primer extension products (col. 3, lines 4-8), and

(B) priming the denatured strands with a set of unmodified or modified primers specific to and hybridizable with opposing strands of each target nucleic acid to be amplified, by cooling to a second temperature, T2 (col. 3, lines 9-12), and

(C) either as a continuation of step (B) or in a separate step, forming primer extension products in a reaction mixture of PCR reagents, by incubation at a third temperature, T3, provided that

when priming and primer extension product formation are carried out in the same step, T2 and T3 are the same (col. 3, lines 13-18),

wherein the reaction mixture in at least one of the primary amplification cycles comprises from 1 to 20 weight %, preferably from 1 to 15 weight % and most preferably from 1 to 8 weight % of a nonionic polymeric volume exclusion agent (col. 3, lines 19-21, where the disclosed percentage of 4 weight % falls within the range(s) claimed), and a hot start DNA polymerase (col. 7, lines 11-19, where the inclusion of a polymerase and the inclusion of an antibody specific to the DNA polymerase which inhibits enzymatic activity below about 50°C and which is inactivated at higher temperatures).

With regard to claim 2 and 4, Backus teaches a method for the coamplification of two or more target nucleic acids having different sequence compositions, said method comprising at least 15 primary amplification cycles (col. 3, lines 22-26), each amplification cycle comprising the sequential steps of:

(A) heating a reaction mixture of two or more target nucleic acids, or their primer extension products, at a first temperature, T1, for denaturation of the strands of the target nucleic acids or their primer extension products (col. 3, lines 27-31), and

(B) priming the denatured strands with a set of unmodified or modified primers specific to and hybridizable with opposing strands of each target nucleic acid to be amplified, by cooling to a second temperature, T2 (col. 3, lines 32-35), and

(C) either as a continuation of step (B) or in a separate step, forming primer extension products in a reaction mixture of PCR reagents, by incubation at a third temperature, T3, provided that

when priming and primer extension product formation are carried out in the same step, T2 and T3 are the same (col. 3, lines 36-41),

wherein the reaction mixture in at least one of the primary amplification cycles comprises from 1 to 20 weight, preferably from 1 to 15 weight % and most preferably from 1 to 8 weight % of a nonionic, polymeric volume exclusion agent (col. 3, lines 42-45, wherein the disclosed percentage of 4 weight % falls within the claimed range(s)), and a DNA polymerase or a hot start DNA polymerase (col. 7, lines 11-19, where the inclusion of a polymerase and the inclusion of an antibody specific to the DNA polymerase which inhibits enzymatic activity below about 50°C and which is inactivated at higher temperatures), and

(D) in the course of the reaction in each amplification cycle or in an amplification cycle after the last primary amplification cycle, detecting one or more of the primer extension products as an indication of one or more of the target nucleic acids (col. 3, lines 46-48).

With regard to claim 5, Backus teaches a method according to one of claims 1 - 4, characterized in that the volume exclusion agent is selected from the group consisting of a polyether, a reaction product of a sugar with epichlorohydrin, a polysaccharide, and a polyacrylate (col. 7, lines 36-41).

With regard to claim 6, Backus teaches a method according to claim 5, characterized in that the volume exclusion agent is selected from the group of polyethers of the general formula;

$$H\text{-}(\text{-}O\text{-}R\text{-})_n\text{-}H$$

wherein R is an alkylene bridge of 1 to 6 carbon atoms - branched or unbranched - and n is an integer of 15 to 1000 (col. 3, lines 42-48).

With regard to claim 7, Backus teaches an embodiment of claim 6, characterized in that

R may represent 1,2-ethylene, 1,3-propylene, 1,2-propylene, 2-hydroxy-1,3-propylene, 3-hydroxy-1,2-propylene, 1,4-butylene, 1,3-butylene, or 1,2-hexylene (col. 7, lines 48-52).

With regard to claim 8, Backus teaches an embodiment of claim 6, characterized in that the polyether is poly(ethylene glycol) (col. 7, lines 53-56, where it is noted that a preferred R group is polyethylene glycol).

With regard to claim 9, Backus teaches an embodiment of claim 8, characterized in that the polytethylene glycol) has a molecular weight in the range of 1000 to 2,000,000 (col. 7, lines 59-67, where it is noted that the preferred range is between about 1000 to about 20,000, wherein the term about represents +/-10% and wherein the preferred range of molecular weights falls within the range as claimed, presuming that it is intended for the claimed ranges to be measured in daltons; col. 15, lines 19-21, where PEG-8000, a polyethylene glycol with a molecular weight of 8000 daltons was used in the examples).

With regard to claim 10, Backus teaches an embodiment of claim 8, characterized in that the poly(ethylene glycol) has a molecular weight in the range of 3000 to 500,000 (col. 7, lines 59-67, where it is noted that the preferred range is between about 1000 to about 20,000, wherein the term about represents +/-10% and wherein the preferred range of molecular weights falls within the range as claimed, presuming that it is intended for the claimed ranges to be measured in daltons; col. 15, lines 19-21, where PEG-8000, a polyethylene glycol with a molecular weight of 8000 daltons was used in the examples).

With regard to claim 11, Backus teaches an embodiment of claim 8, characterized in that the poly(ethylene glycol) has a molecular weight of about 8000 (col. 7, lines 59-67, where it is noted that the preferred range is between about 1000 to about 20,000, wherein the term about

represents +/-10% and wherein the preferred range of molecular weights falls within the range as claimed, presuming that it is intended for the claimed ranges to be measured in Daltons; col. 15, lines 19-21, where PEG-8000, a polyethylene glycol with a molecular weight of 8000 daltons was used in the examples).

With regard to claim 12, Backus teaches an embodiment of claim 5, characterized in that the volume exclusion reagent is a dextran (col. 8, lines 9-11, where dextran is noted as a preferred nonionic polysaccharide).

With regard to claim 13, Backus teaches an embodiment of claim 12, characterized in that the dextran has a molecular weight in the range of 1000 to 2,000,000 (col. 7, lines 30-35, where it is noted that the volume exclusion agents generally have a molecular weight from about 1000 to about 20,000 daltons, wherein the disclosed range falls within the range as claimed).

With regard to claim 14, Backus teaches an embodiment of claim 12, characterized in that the dextran has a molecular weight in the range of 3000 to 500,000 (col. 7, lines 30-35, where it is noted that the volume exclusion agents generally have a molecular weight from about 1000 to about 20,000 daltons, wherein the disclosed range falls within the range as claimed).

With regard to claim 16, Backus teaches an embodiment of claim 5, characterized in that the polyacrylate is selected from the group consisting of poly(hydroxyethyl acrylate) or poly(2,3-dihydroxypropyl acrylate) (col. 8, lines 12-15).

Regarding claims 1-4, Backus does not explicitly teach that the two or more target nucleic acids are present at comparable copy numbers whereas the maximum difference between the lowest and the highest copy number is 10 fold. Regarding claim 2-4, Backus does not teach

that the reaction mixture comprises a sequence specific probe which binds within the primer binding regions and which generates a fluorescent signal after hybridization.

Bustin teaches an overview of the quantitation of mRNA using a variety of methods, including quantitative real-time RT-PCR, a method which incorporates a variety of means of detection, including hybridization probes (Abstract).

With regard to claims 1-4, Bustin teaches the coamplification of nucleic acids which are present at comparable copy numbers, wherein the maximum difference between the lowest and highest copy number is 10-fold (p. 182, col. 1, 2nd paragraph, where the normalization of quantification of a target nucleic acid is accomplished through co-amplification of an internal control target sequence, referred to as an endogenous control. It is also noted that the endogenous control should be expressed at roughly the same level as the RNA under study).

With regard to claims 2-4, Bustin discloses a sequence specific probe which binds within the primer binding regions and which generates a fluorescent signal after hybridization (Figure 3 and p. 174, where molecular beacon probes were described; Figure 4A-C right side and p. 177, where 'hybdrization probes' were described; Figure 5, p. 177, where TaqMan hydrolysis probes were described).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Backus to incorporate the fluorescent hybridization probes and coamplification of a target sequence of comparable copy number the of Bustin, to arrive at the claimed invention with a reasonable expectation for success. As taught by Bustin, "The accepted method for minimizing these errors and correcting for sample-to-sample variation is to amplify, simultaneously with the target, a cellular RNA that serves as an internal

reference against which other RNA values can be normalized. The ideal internal standard should be expressed at a constant level among different tissues of an organism, at all stages of development, and should be unaffected by the experimental treatment. In addition, an exogenous control should also be expressed at roughly the same level as the RNA under study" (p. 182, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to extend the coamplification in the presence of a polymeric volume exclusion agent taught by Backus to incorporate the teachings of Bustin with a reasonable expectation for success in order to achieve quantitative coamplification of two nucleic acid targets of similar copy number.

11. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Backus et al. (US Patent 5,703,366; January 1998) in view of Bustin, SA (Journal of Molecular Endocrinology, 2000, vol. 25, p. 169-193) as applied to claims 1-14 and 16 above, and further in view of Mauzac et al. (US Patent 4,740,594; April 1988), Lantz et al. (Journal of Microbiological Methods, 1997, vol. 28, p. 159-167) as evidenced by JBC Handbook (4^{th} edition, 1997, entry on Dextran 40). Backus discloses a method of amplification of multiple target nucleic acids in the presence of a nonionic, polymeric volume exclusion agent (Abstract).

Backus in view of Bustin teaches all of the limitations of claims 1-14 and 16 as recited in the 103 rejection stated above. However, Backus does not explicitly disclose the use of dextran within the molecular weight range of 40,000 to 60,000.

With regard to claim 15, Lantz teaches an embodiment of claim 12, characterized in that

the dextran has a molecular weight in the range of 40,000 to 60,000 (p. 161, col. 1, 'preparation of aqueous two-phase system' heading, where Dextran 40 and PEG 4000 were used in a two-phase system for purification of PCR reactions; and see 'Dextran 40' entry from the JBC Handbook for the molecular weight, at 40,000 daltons).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Backus and Bustin to incorporate the specific molecular weight of dextran disclosed by Lantz and Mauzac to arrive at the claimed invention with a reasonable expectation for success. As stated by Mauzac, "Dextran is a polyglucoside of molecular weight from about 5000 to several millions of daltons, formed by glycosyl units A with linkages..." (col. 1, lines 65-67). As noted by Mauzac, dextran is a molecule that is present in a wide variety of molecular weights. While Lantz does not include the dextran of 40,000 daltons as an additive in coamplification, the disclosure of an alternate molecular weight within the range renders the claimed range of molecular weights obvious because considering the teachings of Mauzac and Lantz, one of ordinary skill in the art would have been motivated to incorporate dextran molecules of higher molecular weights than 20,000 daltons as disclosed by Backus to incorporate additional molecular weights.

Furthermore, an ordinary practitioner would have recognized that the results optimizable variables of the concentration or specific molecular weight of the nonionic polymeric volume exclusion agent could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephanie K Mummert, Ph.D.

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SKM

Examiner
Art Unit 1637

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

8/7/06